Remarks

The Office Action mailed April 5, 2002 has been received and reviewed. The finality of the Office Action will be removed by the Request For Continued Examination filed with this Amendment. Claims 1 through 3, 5 through 11 and 14 through 18 are pending. All claims stand rejected. Applicants have canceled claims 1-3, 5, 15 and 16, without prejudice or disclaimer. Claims 6, 7, 14, 14, 17 and 18 are amended herein. Reconsideration of the application as amended is respectfully requested.

Applicants note the objections to the claims, specifications and drawings have been withdrawn. Applicants further note the withdrawal of the rejection of claims on various grounds stated in the prior Office Action. The attention of the Examiner to the application is appreciated. The remaining and newly presented rejections are addressed below.

The renumbering of claims 12-16 to 14 to 18 in the Office Action is noted. Applicants have amended claims 17 and 18 to ensure the proper change in dependency is maintained.

Claim 14 was objected to due to a typographical error. Claim 14 has been amended to correct the spelling of *typhi* and applicants respectfully submit no further action is required on this point.

35 U.S.C. § 112 Rejections

The rejection of claim 6 under 35 U.S.C. §112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention was maintained from the earlier Office Action.

The Office Action Made Final states that "Applicant's does not refer to a deposit of *Salmonella* strain 108955 in the specification, therefore there is no assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met." Applicants respectfully submit that the specification refers to the deposit of *Salmonella typhimurium* STM 2001 in the specification on page 17, lines 9-11. It is gratefully noted that the amendment to refer to the current address of the *Centraalbureau voor Schimmelcultures* was entered. The Office Action appears to confuse the strain number with the accession number for the deposit. A copy of the receipt for the deposit and a viability statement are included with this Amendment to verify the

deposit. A Budapest Treaty declaration has been prepared and a signed copy of the declaration will be forwarded to the Office upon receipt. Withdrawal of this rejection is thus requested.

35 U.S.C. § 102 Rejections

Claims 1-3, 6-7 and 11 were rejected in the Office Action Made Final as allegedly anticipated by the journal article: Virulence of *Salmonella enterica* serotype Enteritidis aflagellate and afimbriate mutants in a day-old chick model, *Epedemiol. Infect.* (1999) 122, 395-402 to Allen-Vercoe et al. (hereinafter "Allen-Vercoe"). Claims 1-3 have been canceled rendering this rejection moot asa to them.

The Office Action Made Final states: "Allen-Vercoe et al teach a *Salmonella enteriditis* mutated bacterium that in its wild type form carries flagella and said mutated bacterium lacking at least one determinant of flagellin or flagella found in its wild form. Allen-Vercoe et al teach that isolated bacteria colonies were diluted using phospate buffered saline and the inocula were administered immediately (page 396, 2nd column)." Allen-Vercoe describes an experimental study into the behavior of colonization and invasion of flagella- and/or fimbriae-less *Salmonella enteritidis* mutants in chicken. The main conclusion reached is that "flagella . . . played an important role in the pathogenesis of Enteritidis ...." (Allen-Vercoe at page 400). However, it does not disclose the use of flagella-less mutants as a vaccine.

As amended, claim 6 includes the elements of a"mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form and having the same immunological characteristics as the bacterium strain that has been deposited with the Centraalbureau voor Schimmelcultures under accession-number CBS 108995". Applicants note that Allen-Vercoe does not discuss antigenic determinants at all. It is thus respectfully submitted that claim 6 is not anticipated by Allen-Vercoe and this rejection should be withdrawn.

Claim 7, as amended, is directed to a vaccine and similarly includes the elements of "said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form." Applicant submits this rejection should be withdrawn and the claim allowed on this basis alone. Further, the section of Allen-Vercoe cited in the Office Action Made Final (page 396, column 2) describes not a vaccine, but an inoculum for the study of colonization and invasion. The

induction of a protective immune response, which is a critical feature of a vaccine, is not mentioned. The inoculated animals were sacrificed for dissection to examine colonization, not examined for immune protection. Applicants respectfully submit that claim 7 defines over the cited reference on this basis as well. It is requested that amended claim 7, with claim 11 dependent therefrom, be allowed.

Claims 1-3, and 5- 11 were rejected in the Office Action Made Final as allegedly anticipated by WO 89/10967 to Marjarian et al (hereinafter "Marjarian"). Claims 1-3 and 5 have been canceled rendering this rejection moot as to them. Applicants respectfully traverse this rejection as to claims 6 and 7 and the claims dependent therefrom.

Marjarian is directed to bacteria carrying recombinant flagella carrying heterologous epitopes. Vaccines disclosed therein either consist of subunit flagellar proteins or of live attenuated bacteria expressing flagella from recombinant plasmids. The Office Action Made Final states that: "Marjarian et al teach the use of a live attenuated *Salmonella dubin* strain (SL5927) that is non-flagellated (and thus non-motile) and lacks at least one antigenic determinant of flagellin or flagella found in its wild form (pages 59 and 66-67)."

However, the Marjarian approach requires that the flagellin gene be present. Marjarian page 11, lines 26-30, states: "The recombinant flagellin proteins are exported to the cell surface, wherein a preferred embodiment, they assemble into functional flagella containing the heterologous epitope." Marjarian thus does not disclose flagellin minus bacteria as vaccines *per se.* Rather these bacteria are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene-construct. Applicants thus submit that amended claim 6 and amended claim 7, with claims 8-11 dependent therefrom, define over this reference and request they be allowed.

Claims 14, 16 and 18 were rejected in the Office Action Made Final as allegedly anticipated by GB 1,109,179 to Anderson (hereinafter "Anderson"). Claim 16 has been canceled rendering this rejection moot as to it. Anderson is directed to a killed, human vaccine for parenteral use. As discussed at page 2, lines 53 to 55; page 3, lines 49 to 86 and claim 1 of Anderson, the vaccines disclosed therein all use killed flagella-less bacteria. As amended, claim 14 is directed to a "live

attenuated vaccine" and applicants submit it thus defines over Anderson and request it be allowed. Claim 18 depends from claim 14 and should similarly be allowed.

Claims 14-18 were rejected in the Office Action Made Final as allegedly anticipated by WO 89/10967 to Marjarian et al (hereinafter "Marjarian"). Claims 15 and 16 have been canceled rendering this rejection moot as to them. Applicants respectfully submit that as amended, claim 14, with claims 17 and 18 dependent therefrom, defines over Marjarian.

As has been discussed earlier herein, Marjarian is directed to bacteria carrying recombinant flagella carrying heterologous epitopes. The Office Action Made Final notes that: "Marjarian et al teach attenuated invasive bacteria expressing the recombinant flagellin genes of the [Marjarian] invention used in live vaccine formulations" (Office Action Made Final at page 9). As discussed previously herein, vaccines disclosed in Marjarian either consist of subunit flagellar proteins or of live attenuated bacteria expressing flagella from recombinant plasmids. The Marjarian approach requires that the flagellin gene be present. Marjarian page 11, lines 26-30, states: "The recombinant flagellin proteins are exported to the cell surface, wherein a preferred embodiment, they assemble into functional flagella containing the heterologous epitope." Marjarian thus does not disclose flagellin minus bacteria as vaccines *per se*. Rather these bacteria are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene construct. Applicant thus submits that amended claim 14, with claims 17 and 18 dependent therefrom, define over this reference and request they be allowed.

Conclusion

In view of the amendments and remarks, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicant's attorney at the address or telephone number given herein.

Respectfully submitted,

Bretton L. Crockett
Registration No. 44,632
Attorney for Applicant
TRASK BRITT PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

Date: October 7, 2002
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VERSION WITH MARKINGS SHOWING CHANGES MADE

6. (Three Times Amended) [The] A mutated bacterium [according to claim 1,] that in its wild type form carries flagella, said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form and having the same immunological characteristics as the bacterium strain that has been deposited with the Centraalbureau voor Schimmelcultures under accession-number CBS 108995.

7. (Two Times Amended) [Vaccine] A vaccine for the protection of animals against Salmonellosis, comprising an immunologically effective amount of [bacteria as defined in claim 1] a mutated bacterium or antigenic material thereof and a pharmaceutically acceptable carrier said mutated bacterium being selected from the group consisting of the *Salmonella* species *typhimurium, enteritidis, choleraesuis, dublin, abortus-ovi, abortus-equi, derby, hadar, heidelberg, agona,* and *arizonae,* that in its wild type form carries flagella, said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form.

14. (Amended) A live attenuated vaccine for the protection of a subject against Salmonellosis comprising an immunologically effective amount of a mutated bacterium or mutagenic material thereof and a pharmaceutically acceptable carrier, said mutated bacterium being selected from the group consisting of the *Salmonella* species [*tyhpi*] *typhi* and *paratyphi A* and *B*, that in its wildtype form carries flagella, said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wildtype form [, or an antigenic material thereof and a pharmaceutically acceptable carrier].

17. (Amended) The vaccine according to claim [12] 14, comprising an adjuvant.

18. (Amended) The vaccine according to claim [12] 14, in a freeze-dried or spray-dried form.